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09/264,585 **8 March 1999 (08.03.1999) US**

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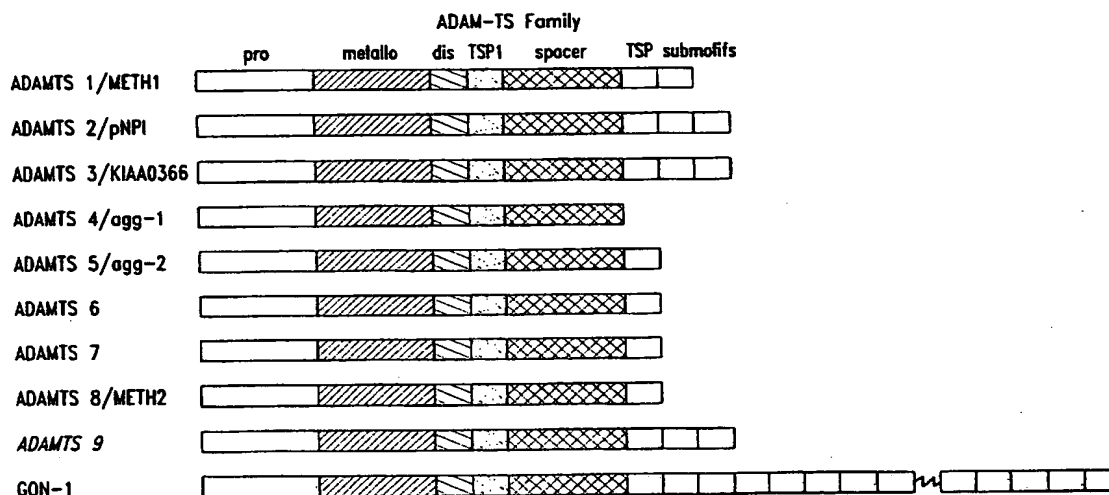
Published:

— With international search report.

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18 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **METALLOPROTEINASES AND METHODS OF USE THEREFOR**



(57) Abstract: Members of the ADAMTS family of metalloproteinases are provided, along with variants thereof and agents that modulate an activity of such metalloproteinases. The polypeptides and modulating agents may be used, for example, in the prevention and treatment of a variety of conditions associated with undesirable levels of metalloproteinase activity.

INTERNATIONAL SEARCH REPORT

International Application No

P /US 00/06237

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/57 C12N15/63 C12N9/64 A61K38/48 C07K16/40
C12Q1/37

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K C07K C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 55643 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 10 December 1998 (1998-12-10) & EP 1 004 674 A (KUREHA CHEMICAL INDUSTRY CO., LTD.) 31 May 2000 (2000-05-31) --- -/--	1,3-11, 17-21, 28,29, 31,32

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

29 June 2000

Date of mailing of the international search report

13.10.00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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MONTERO LOPEZ B.

INTERNATIONAL SEARCH REPORT

International Application No

P../US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KOUJI KUNO ET AL.: "Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene"</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 1, 3 January 1997 (1997-01-03), pages 556-562, XP002076038</p> <p>MD US</p> <p>cited in the application abstract</p> <p>page 558, left-hand column, paragraph 2</p> <p>-page 559, left-hand column, paragraph 2; figure 2</p> <p>page 559, left-hand column, paragraph 4</p> <p>page 561, right-hand column, last paragraph</p> <p>-page 562, left-hand column, paragraph 1</p>	1,3-11, 17,20, 21,28, 29,31,32
X	<p>---</p> <p>KOUJI KUNO ET AL.: "The exon/intron organization and chromosomal mapping of the mouse ADAMTS-1 gene encoding an ADAM family protein with TPS motifs"</p> <p>GENOMICS, vol. 46, no. 3, 15 December 1997 (1997-12-15), pages 466-471, XP000922766</p> <p>cited in the application</p> <p>page 466, right-hand column, paragraph 2</p> <p>page 468, left-hand column, paragraph 5</p> <p>-page 470, right-hand column, paragraph 2; figure 3</p>	1,3-11
X	<p>---</p> <p>BOR LUEN TANG ET AL.: "ADAMTS: A novel family of proteases with an ADAM protease domain and thrombospondin 1 repeats"</p> <p>FEBS LETTERS, [Online]</p> <p>vol. 445, 26 February 1999 (1999-02-26), pages 223-225, XP002141413</p> <p>AMSTERDAM NL</p> <p>Retrieved from the Internet:</p> <p><URL:http://gdbwww.gdb.org/gdb-bin/genera/genera/hgd/Gene?!action=query&displayName=ADAMTS2> [retrieved on 2000-06-22]</p> <p>page 223, left-hand column, paragraph 2</p> <p>-page 225, right-hand column, paragraph 2; figure 2</p>	1,3-11
X	<p>---</p> <p>EMBL Database Entry AI378857</p> <p>Accession number AI378857; 28 January 1999</p> <p>ROBERT STRAUSBERG:"tc67h11.x1</p> <p>Soares_NhMMPu_S1 Homo sapiens cDNA clone"</p> <p>XP002141415</p> <p>the whole document</p> <p>---</p> <p>-/--</p>	1,5-7

INTERNATIONAL SEARCH REPORT

International Application No

P /US 00/06237

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>FRANCISCA VÁZQUEZ ET AL.: "METH-1, a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 33, 13 August 1999 (1999-08-13), pages 23349-23357, XP002141414 MD US abstract page 23349, right-hand column, paragraph 2 -page 23350, left-hand column, paragraph 1 page 23351, left-hand column, paragraph 1 -page 23352, right-hand column, paragraph 2; figure 1 page 23353, left-hand column, paragraph 4 -page 23357, left-hand column, paragraph 2 -----</p>	1,3-6, 8-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/06237

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 22-27, 30, 33-35
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims 1-12, 17-35 (partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 22-27, 30, 33-35

Present claims 22-27, 30 and 33-35 relate to an agent defined by reference to a desirable characteristic or property, namely decreasing or modulating expression or activity of an ADAMTS protein. The claims cover all agents having this characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any specific example of such agents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the agent by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 22-27, 30 and 33-35.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:1 or 23 encoding ADAMTS-2; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-2 polypeptide; ADAMTS-2 polypeptide of SEQ ID NO:2 or 24 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-2 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-2 protein

2. Claims: 36 and partially 1-12, 17-35

Polynucleotide of SEQ ID NO:3, 15 or 17 encoding ADAMTS-4; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-4 polypeptide; ADAMTS-4 polypeptide of SEQ ID NO:4, 16 or 18 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-4 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-4 protein

3. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:9 or 25 encoding ADAMTS-3; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-3 polypeptide; ADAMTS-3 polypeptide of SEQ ID NO:10 or 26 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-3 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-3 protein

4. Claims: Partially 1-12, 17-35

Polynucleotide of SEQ ID NO:13 or 21 encoding ADAMTS-5; vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-5 polypeptide; ADAMTS-5 polypeptide of SEQ ID NO:13 or 21 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-5 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-5 protein

5. Claims: Partially, 1, 3-12, 17-35

Polynucleotide encoding an ADAMTS-9 protein of SEQ ID NO:27;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

vector and host cell comprising the same; complementary antisense molecule; use of the polynucleotide for preparing an ADAMTS-9 polypeptide; ADAMTS-9 polypeptide of SEQ ID NO:27 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS-9 polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS-9 protein

6. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:6 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:6 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

7. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:8 or a variant thereof; ADAMTS polypeptide of SEQ ID NO:8 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

8. Claims: Partially 8, 13-35

Method of preparing an ADAMTS polypeptide by culturing a transfected cell comprising a polynucleotide encoding a polypeptide of SEQ ID NO:12 or 20 or variants thereof; ADAMTS polypeptide of SEQ ID NO:12 or 20 and variants thereof; pharmaceutical composition and vaccine comprising the same; antibody binding to the polypeptide; use of the ADAMTS polynucleotide and polypeptide in screening methods and agents modulating the activity of the ADAMTS protein

Information on patent family members

F ./US 00/06237

Form PCT/ISA/210 (patent family annex) (July 1992)


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<210> 8

<211> 1201

<212> PRT

<213> Homo sapien

<400> 8

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Lys Arg Tyr Arg Glu Tyr Glu Leu Val Thr Pro Val Ser Thr Asn Leu
      35             40             45
Glu Gly Arg Tyr Leu Ser His Thr Leu Ser Ala Ser His Lys Lys Arg
      50             55             60
Ser Ala Arg Asp Val Ser Ser Asn Pro Glu Gln Leu Phe Phe Asn Ile
      65             70             75             80
Thr Ala Phe Gly Lys Asp Phe His Leu Arg Leu Lys Pro Asn Thr Gln
      85             90             95

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Leu Val Ala Pro Gly Ala Val Val Glu Trp His Glu Thr Ser Leu Val
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 Pro Gly Asn Ile Thr Asp Pro Ile Asn Asn His Gln Pro Gly Ser Ala
 115 120 125
 Thr Tyr Arg Ile Arg Lys Thr Glu Pro Leu Gln Thr Asn Cys Ala Tyr
 130 135 140
 Val Gly Asp Ile Val Asp Ile Pro Gly Thr Ser Val Ala Ile Ser Asn
 145 150 155 160
 Cys Asp Gly Leu Ala Gly Met Ile Lys Ser Asp Asn Glu Glu Tyr Phe
 165 170 175
 Ile Glu Pro Leu Glu Arg Gly Lys Gln Met Glu Glu Glu Lys Gly Arg
 180 185 190
 Ile His Val Val Tyr Lys Arg Ser Ala Val Glu Gln Ala Pro Ile Asp
 195 200 205
 Met Ser Lys Asp Phe His Tyr Arg Glu Ser Asp Leu Glu Gly Leu Asp
 210 215 220
 Asp Leu Gly Thr Val Tyr Gly Asn Ile His Gln Gln Leu Asn Glu Thr
 225 230 235 240
 Met Arg Arg Arg Arg His Ala Gly Glu Asn Asp Tyr Asn Ile Glu Val
 245 250 255
 Leu Leu Gly Val Asp Asp Ser Val Val Arg Phe His Gly Lys Glu His
 260 265 270
 Val Gln Asn Tyr Leu Leu Thr Leu Met Asn Ile Val Asn Glu Ile Tyr
 275 280 285
 His Asp Glu Ser Leu Gly Val His Ile Asn Val Val Leu Val Arg Met
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 Ile Met Leu Gly Tyr Ala Lys Ser Ile Ser Leu Ile Glu Arg Gly Asn
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 Pro Ser Arg Ser Leu Glu Asn Val Cys Arg Trp Ala Ser Gln Gln Gln
 325 330 335
 Arg Ser Asp Leu Asn His Ser Glu His His Asp His Ala Ile Phe Leu
 340 345 350
 Thr Arg Gln Asp Phe Gly Pro Ala Gly Met Gln Gly Tyr Ala Pro Val
 355 360 365
 Thr Gly Met Cys His Pro Val Arg Ser Cys Thr Leu Asn His Glu Asp
 370 375 380
 Gly Phe Ser Ser Ala Phe Val Val Ala His Glu Thr Gly His Val Leu
 385 390 395 400
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 405 410 415
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 420 425 430
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 435 440 445
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 450 455 460
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 465 470 475 480
 Asp Phe Gly Val Gly Tyr Lys Met Cys Thr Ala Phe Arg Thr Phe Asp
 485 490 495
 Pro Cys Lys Gln Leu Trp Cys Ser His Pro Asp Asn Pro Tyr Phe Cys
 500 505 510
 Lys Thr Lys Lys Gly Pro Pro Leu Asp Gly Thr Glu Cys Ala Ala Gly
 515 520 525
 Lys Trp Cys Tyr Lys Gly His Cys Met Trp Lys Asn Ala Asn Gln Gln

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Lys Gln Asp Gly Asn Trp Gly Ser Trp Thr	Lys Phe Gly Ser Cys Ser	
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Pro Met Pro Ile Asn Gly Gly Gln Asp Cys Pro	Gly Val Asn Phe Glu	
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Tyr Gln Leu Cys Asn Thr Glu Glu Cys Gln Lys	His Phe Glu Asp Phe	
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Arg Ala Gln Gln Cys Gln Gln Arg Asn Ser His	Phe Glu Tyr Gln Asn	
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Thr Lys His His Trp Leu Pro Tyr Glu His Pro	Asp Pro Lys Lys Arg	
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Cys His Leu Tyr Cys Gln Ser Lys Glu Thr Gly	Asp Val Ala Tyr Met	
645	650	655
Lys Gln Leu Val His Asp Gly Thr His Cys Ser	Tyr Lys Asp Pro Tyr	
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Ser Ile Cys Val Arg Gly Glu Cys Val Lys Val	Gly Cys Asp Lys Glu	
675	680	685
Ile Gly Ser Asn Lys Val Glu Asp Lys Cys Gly	Val Cys Gly Gly Asp	
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Asn Ser His Cys Arg Thr Val Lys Gly Thr Phe	Thr Arg Thr Pro Arg	
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Lys Leu Gly Tyr Leu Lys Met Phe Asp Ile Pro	Pro Gly Ala Arg His	
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Val Leu Ile Gln Glu Asp Glu Ala Ser Pro His	Ile Leu Ala Ile Lys	
740	745	750
Asn Gln Ala Thr Gly His Tyr Ile Leu Asn Gly	Lys Gly Glu Glu Ala	
755	760	765
Lys Ser Arg Thr Phe Ile Asp Leu Gly Val Glu	Trp Asp Tyr Asn Ile	
770	775	780
Glu Asp Asp Ile Glu Ser Leu His Thr Asp Gly	Pro Leu His Asp Pro	
785	790	795
Val Ile Val Leu Ile Ile Pro Gln Glu Asn Asp	Thr Arg Ser Ser Leu	
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Thr Tyr Lys Tyr Ile Ile His Glu Asp Ser Val	Pro Thr Ile Asn Ser	
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Asn Asn Val Ile Gln Glu Glu Leu Asp Thr Phe	Glu Trp Ala Leu Lys	
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Ser Trp Ser Gln Val Ser Lys Pro Cys Gly Gly	Gly Phe Gln Tyr Thr	
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Lys Tyr Gly Cys Arg Arg Lys Ser Asp Asn Lys	Met Val His Arg Ser	
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Phe Cys Glu Ala Asn Lys Lys Pro Lys Pro Ile	Arg Arg Met Cys Asn	
885	890	895
Ile Gln Glu Cys Thr His Pro Leu Trp Val Ala	Glu Glu Trp Glu His	
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Cys Thr Lys Thr Cys Gly Ser Ser Gly Tyr Gln	Leu Arg Thr Val Arg	
915	920	925
Cys Leu Gln Pro Leu Leu Asp Gly Thr Asn Arg	Ser Val His Ser Lys	
930	935	940
Tyr Cys Met Gly Asp Arg Pro Glu Ser Arg Arg	Pro Cys Asn Arg Val	
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Pro Cys Pro Ala Gln Trp Lys Thr Gly Pro Trp	Ser Glu Cys Ser Val	
965	970	975

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 Asp His Cys Asp Gly Glu Lys Pro Glu Ser Val Arg Ala Cys Gln Leu
 995 1000 1005
 Pro Pro Cys Asn Asp Glu Pro Cys Leu Gly Asp Lys Ser Ile Phe Cys
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 Gln Met Glu Val Leu Ala Arg Tyr Cys Ser Ile Pro Gly Tyr Asn Lys
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 Leu Cys Cys Glu Ser Cys Ser Lys Arg Ser Ser Thr Leu Pro Pro Pro
 1045 1050 1055
 Tyr Leu Leu Glu Ala Ala Glu Thr His Asp Asp Val Ile Ser Asn Pro
 1060 1065 1070
 Ser Asp Leu Pro Arg Ser Leu Val Met Pro Thr Ser Leu Val Pro Tyr
 1075 1080 1085
 His Ser Glu Thr Pro Ala Lys Lys Met Ser Leu Ser Ser Ile Ser Ser
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 Asp Gly Ala Asn Leu Arg Gln Arg Ser Ala Gln Gln Ala Gly Ser Lys
 1125 1130 1135
 Thr Val Arg Leu Val Thr Val Pro Ser Ser Pro Pro Thr Lys Arg Val
 1140 1145 1150
 His Leu Ser Ser Ala Ser Gln Met Ala Ala Ala Ser Phe Phe Ala Ala
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 <211> 2868
 <212> DNA
 <213> Homo sapien

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<210> 10

<211> 958

<212> PRT

<213> Homo sapien

<400> 10

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Gly Asp Tyr Phe Ile Glu Pro Leu Gln Ser Met Asp Glu Gln Glu Asp
      35           40           45
Glu Glu Glu Gln Asn Lys Pro His Ile Ile Tyr Arg Arg Ser Ala Pro
      50           55           60
Gln Arg Glu Pro Ser Thr Gly Arg His Ala Cys Asp Thr Ser Glu His
      65           70           75           80
Lys Asn Arg His Ser Lys Asp Lys Lys Lys Thr Arg Ala Arg Lys Trp
      85           90           95
Gly Glu Arg Ile Asn Leu Ala Gly Asp Val Ala Ala Leu Asn Ser Gly
      100          105          110
Leu Ala Thr Glu Ala Phe Ser Ala Tyr Gly Asn Lys Thr Asp Asn Thr
      115          120          125
Arg Glu Lys Arg Thr His Arg Arg Thr Lys Arg Phe Leu Ser Tyr Pro
      130          135          140

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Arg Phe Val Glu Val Leu Val Val Ala Asp Asn Arg Met Val Ser Tyr
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 His Gly Glu Asn Leu Gln His Tyr Ile Leu Thr Leu Met Ser Ile Asp
 165 170 175
 Gly Pro Ser Ile Ser Phe Asn Ala Gln Thr Thr Leu Lys Asn Leu Cys
 180 185 190
 Gln Trp Gln His Ser Lys Asn Ser Pro Gly Gly Ile His His Asp Thr
 195 200 205
 Ala Val Leu Leu Thr Arg Gln Asp Ile Cys Arg Ala His Asp Lys Cys
 210 215 220
 Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr Ile Cys Asp Pro Tyr Arg
 225 230 235 240
 Ser Cys Ser Ile Ser Glu Asp Ser Gly Leu Ser Thr Ala Phe Thr Ile
 245 250 255
 Ala His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Asn Asn
 260 265 270
 Lys Cys Lys Glu Glu Gly Val Lys Ser Pro Gln His Val Met Ala Pro
 275 280 285
 Thr Leu Asn Phe Tyr Thr Asn Pro Trp Met Trp Ser Lys Cys Ser Arg
 290 295 300
 Lys Tyr Ile Thr Glu Phe Leu Asp Thr Gly Tyr Gly Glu Cys Leu Leu
 305 310 315 320
 Asn Glu Pro Glu Ser Arg Pro Tyr Pro Leu Pro Val Gln Leu Pro Gly
 325 330 335
 Ile Leu Tyr Asn Val Asn Lys Gln Cys Glu Leu Ile Phe Gly Pro Gly
 340 345 350
 Ser Gln Val Cys Pro Tyr Met Met Gln Cys Arg Arg Leu Trp Cys Asn
 355 360 365
 Asn Val Asn Gly Val His Lys Gly Cys Arg Thr Gln His Thr Pro Trp
 370 375 380
 Ala Asp Gly Thr Glu Cys Glu Pro Gly Lys His Cys Lys Tyr Gly Phe
 385 390 395 400
 Cys Val Pro Lys Glu Met Asp Val Pro Val Thr Asp Gly Ser Trp Gly
 405 410 415
 Ser Trp Ser Pro Phe Gly Thr Cys Ser Arg Thr Cys Gly Gly Gly Ile
 420 425 430
 Lys Thr Ala Ile Arg Glu Cys Asn Arg Pro Glu Pro Lys Asn Gly Gly
 435 440 445
 Lys Tyr Cys Val Gly Arg Arg Met Lys Phe Lys Ser Cys Asn Thr Glu
 450 455 460
 Pro Cys Leu Lys Gln Lys Arg Asp Phe Arg Asp Glu Gln Cys Ala His
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 485 490 495
 Trp Val Pro Lys Tyr Ser Gly Ile Leu Met Lys Asp Arg Cys Lys Leu
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 Phe Cys Arg Val Ala Gly Asn Thr Ala Tyr Tyr Gln Leu Arg Asp Arg
 515 520 525
 Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 530 535 540
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 545 550 555 560
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 565 570 575
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr

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Ser	Lys	Gly	Glu	Phe	Leu	Leu	Asn	Gly	Asn	Phe	Val	Val	Thr	Met	Ala		
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Lys	Arg	Glu	Ile	Arg	Ile	Gly	Asn	Ala	Val	Val	Glu	Tyr	Ser	Gly	Ser		
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Leu	Leu	Leu	Gln	Val	Leu	Ser	Val	Gly	Lys	Leu	Tyr	Asn	Pro	Asp	Val		
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Arg	Tyr	Ser	Phe	Asn	Ile	Pro	Ile	Glu	Asp	Lys	Pro	Gln	Gln	Phe	Tyr		
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Trp	Asn	Ser	His	Gly	Pro	Trp	Gln	Ala	Cys	Ser	Lys	Pro	Cys	Gln	Gly		
705				710						715					720		
Glu	Arg	Lys	Arg	Lys	Leu	Val	Cys	Thr	Arg	Glu	Ser	Asp	Gln	Leu	Thr		
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Val	Ser	Asp	Gln	Arg	Cys	Asp	Arg	Leu	Pro	Gln	Pro	Gly	His	Ile	Thr		
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Glu	Pro	Cys	Gly	Thr	Asp	Cys	Asp	Leu	Arg	Trp	His	Val	Ala	Ser	Arg		
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Ser	Glu	Cys	Ser	Ala	Gln	Cys	Gly	Leu	Gly	Tyr	Arg	Thr	Leu	Asp	Ile		
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Tyr	Cys	Ala	Lys	Tyr	Ser	Arg	Leu	Asp	Gly	Lys	Thr	Glu	Lys	Val	Asp		
785					790					795					800		
Asp	Gly	Phe	Cys	Ser	Ser	His	Pro	Lys	Pro	Ser	Asn	Arg	Glu	Lys	Cys		
			805						810					815			
Ser	Gly	Glu	Cys	Asn	Thr	Gly	Gly	Trp	Arg	Tyr	Ser	Ala	Trp	Thr	Glu		
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Cys	Ser	Lys	Ser	Cys	Asp	Gly	Gly	Thr	Gln	Arg	Arg	Arg	Ala	Ile	Cys		
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Val	Asn	Thr	Arg	Asn	Asp	Val	Leu	Asp	Asp	Ser	Lys	Cys	Thr	His	Gln		
	850					855					860						
Glu	Lys	Val	Thr	Ile	Gln	Arg	Cys	Ser	Glu	Phe	Pro	Cys	Pro	Gln	Trp		
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Lys	Ser	Gly	Asp	Trp	Ser	Glu	Cys	Leu	Val	Thr	Cys	Gly	Lys	Gly	His		
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<211> 4303
<212> DNA
<213> Homo sapien
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<210> 12

<211> 840

<212> PRT

<213> Homo sapien

<400> 12

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Trp Leu Val Trp Leu Leu Leu Leu Leu Ala Ser Leu Leu Pro Ser
35          40          45
Ala Arg Leu Ala Ser Pro Leu Pro Arg Glu Glu Glu Ile Val Phe Pro
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Glu Lys Leu Asn Gly Ser Val Leu Pro Gly Ser Gly Thr Pro Ala Arg
65          70          75          80
Leu Leu Cys Arg Leu Gln Ala Phe Gly Glu Thr Leu Leu Leu Glu Leu
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Glu Gln Asp Ser Gly Val Gln Val Glu Gly Leu Thr Val Gln Tyr Leu
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Gly Gln Ala Pro Glu Leu Leu Gly Gly Ala Glu Pro Gly Thr Tyr Leu
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Thr Gly Thr Ile Asn Gly Asp Pro Glu Ser Val Ala Ser Leu His Trp
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Asp Gly Gly Ala Leu Leu Gly Val Leu Gln Tyr Arg Gly Ala Glu Leu
145         150         155         160
His Leu Gln Pro Leu Glu Gly Gly Thr Pro Asn Ser Ala Gly Gly Pro
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Gly Ala His Ile Leu Arg Arg Lys Ser Pro Ala Ser Gly Gln Gly Pro
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Met Cys Asn Val Lys Ala Pro Leu Gly Ser Pro Ser Pro Arg Pro Arg
195         200         205
Arg Ala Lys Arg Phe Ala Ser Leu Ser Arg Phe Val Glu Thr Leu Val
210         215         220
Val Ala Asp Asp Lys Met Ala Ala Phe His Gly Ala Gly Leu Lys Arg
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Tyr Leu Leu Thr Val Met Ala Ala Ala Ala Lys Ala Phe Lys His Pro
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 His Leu Pro Val Thr Phe Pro Gly Lys Asp Tyr Asp Ala Asp Arg Gln
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 Met Cys Gln Thr Lys His Ser Pro Trp Ala Asp Gly Thr Pro Cys Gly
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 Pro Ala Gln Ala Cys Met Gly Gly Arg Cys Leu His Met Asp Gln Leu
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 Trp Gly Asp Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Phe Ser Ser
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 610 615 620
 Ala Arg Ala Leu Gly Tyr Tyr Tyr Val Leu Glu Pro Arg Val Val Asp
 625 630 635 640
 Gly Thr Pro Cys Ser Pro Asp Ser Ser Ser Val Cys Val Gln Gly Arg
 645 650 655
 Cys Ile His Ala Gly Cys Asp Arg Ile Ile Gly Ser Lys Lys Lys Phe
 660 665 670
 Asp Lys Cys Met Val Cys Gly Gly Asp Gly Ser Gly Cys Ser Lys Gln
 675 680 685
 Ser Gly Ser Phe Arg Lys Phe Arg Tyr Gly Tyr Asn Asn Val Val Thr

690	695	700
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705	710	715
Gly His Arg Ser Ile Tyr Leu Ala Leu Lys Leu Pro Asp Gly Ser Tyr		
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Ala Leu Asn Gly Glu Tyr Thr Leu Met Pro Ser Pro Thr Asp Val Val		
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Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr Ala Ala Ser		
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Glu Thr Leu Ser Gly His Gly Pro Leu Ala Gln Pro Leu Thr Leu Gln		
	770	775
Val Leu Val Ala Gly Asn Pro Gln Asp Thr Arg Leu Arg Tyr Ser Phe		
	785	790
Phe Val Pro Arg Pro Thr Pro Ser Thr Pro Arg Pro Thr Pro Gln Asp		
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Trp Leu His Arg Arg Ala Gln Ile Leu Glu Ile Leu Arg Arg Arg Pro		
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<210> 13

<211> 1518

<212> DNA

<213> Rattus norvegicus

<400> 13

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<210> 14

<211> 505
 <212> PRT
 <213> Rattus norvegicus

<400> 14

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Ala	Glu	Pro	Asp	Ser	Phe	Ala	Ala	Val	Ser	Leu	Cys	Gly	Gly	Leu	Arg
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Gly	Ala	Phe	Gly	Tyr	Gln	Gly	Ala	Glu	Tyr	Val	Ile	Ser	Pro	Leu	Pro
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Arg	Arg	Ser	Gly	Arg	Ala	Lys	Arg	Phe	Val	Ser	Ile	Pro	Arg	Tyr	Val
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Ala	Asp	Val	Gly	Thr	Met	Cys	Asp	Pro	Lys	Arg	Ser	Cys	Ser	Val	Ile
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Tyr	Met	Gln	Tyr	Cys	Thr	Lys	Leu	Trp	Cys	Thr	Gly	Lys	Ala	Lys	Gly
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 Asn Pro Asn Lys Tyr Arg Val Asp Gly Pro Trp Ala Lys Trp Glu Pro
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<210> 15

<211> 1455

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

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<223> n = A,T,C or G

<400> 15

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<210> 16

<211> 484

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

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<223> Xaa = Any Amino Acid

<400> 16

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Gln	Ile	Leu	Gly	Pro	Glu	Glu	Leu	Pro	Gly	Gln	Thr	Tyr	Asp	Ala	Thr
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Met	Val	Cys	Leu	Thr	Lys	Lys	Leu	Pro	Ala	Val	Glu	Gly	Thr	Pro	Cys
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Gly	Lys	Gly	Arg	Ile	Cys	Leu	Gln	Gly	Lys	Cys	Val	Asp	Lys	Thr	Lys
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Ser	Trp	Gly	Gln	Cys	Ser	Arg	Ser	Cys	Gly	Gly	Gly	Val	Gln	Phe	Ala
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Tyr	Arg	Arg	Cys	Asn	Asn	Pro	Ala	Pro	Arg	Asn	Asn	Gly	Arg	Tyr	Cys
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Tyr	Gln	Ser	Asp	Ala	Lys	Gly	Val	Lys	Thr	Phe	Val	Glu	Trp	Val	Pro
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	290					295					300				
Ile	Pro	Glu	Gly	Ala	Thr	His	Ile	Lys	Val	Arg	Gln	Phe	Lys	Ala	Lys
305					310					315					320
Asp	Gln	Thr	Arg	Phe	Thr	Ala	Tyr	Leu	Ala	Leu	Lys	Lys	Lys	Asn	Gly
				325					330					335	
Glu	Tyr	Leu	Ile	Asn	Gly	Lys	Tyr	Met	Ile	Ser	Thr	Ser	Glu	Thr	Ile
		340						345					350		
Ile	Asp	Ile	Asn	Gly	Thr	Val	Met	Asn	Tyr	Ser	Gly	Trp	Ser	His	Arg
		355					360						365		

Asp Asp Phe Leu His Gly Met Gly Tyr Ser Ala Thr Lys Glu Ile Leu
 370 375 380
 Ile Val Gln Ile Leu Ala Thr Asp Pro Thr Lys Pro Leu Asp Val Arg
 385 390 395 400
 Tyr Ser Phe Phe Val Pro Lys Lys Ser Thr Pro Lys Val Asn Ser Val
 405 410 415
 Thr Ser His Gly Ser Asn Lys Val Gly Ser His Thr Ser Gln Pro Gln
 420 425 430
 Trp Val Thr Gly Pro Trp Leu Ala Cys Ser Arg Thr Cys Asp Thr Gly
 435 440 445
 Trp His Thr Arg Thr Val Gln Cys Gln Asp Gly Asn Arg Lys Leu Ala
 450 455 460
 Lys Gly Cys Pro Leu Ser Gln Arg Pro Ser Ala Phe Lys Gln Cys Leu
 465 470 475 480
 Leu Lys Lys Cys

<210> 17

<211> 423

<212> DNA

<213> Bos taurus

<400> 17

tttagggagg	agcagtgtga	ggccaaaaat	ggatatcagt	ctgatgcaaa	aggagtcaaa	60
acgtttgtgg	aatgggttcc	caaatatgct	ggtgtcctgc	ccggagacgt	gtgcaaactg	120
acctgcagag	ctaagggcac	tggctactac	gtggtgttct	ctccaaaggt	gaccgatggg	180
acagagtgca	ggccatacag	caattccgtg	tgtgtccggg	ggaagtgtgt	gcggacaggc	240
tgtgacagca	tcattggctc	gaagctgcag	tatgacaaat	gtggcgtctg	tggaggagac	300
aactccagtt	gcacaaaggt	ggtcgggaacc	ttcaataaaa	aaagtaaggg	ttacactgac	360
gtcgtgagga	tccccgaagg	ggcgactcac	ataaaagtcc	gacagttcaa	agccaaagac	420
cag						423

<210> 18

<211> 141

<212> PRT

<213> Bos taurus

<400> 18

Phe Arg Glu Glu Gln Cys Glu Ala Lys Asn Gly Tyr Gln Ser Asp Ala
 1 5 10 15
 Lys Gly Val Lys Thr Phe Val Glu Trp Val Pro Lys Tyr Ala Gly Val
 20 25 30
 Leu Pro Gly Asp Val Cys Lys Leu Thr Cys Arg Ala Lys Gly Thr Gly
 35 40 45
 Tyr Tyr Val Val Phe Ser Pro Lys Val Thr Asp Gly Thr Glu Cys Arg
 50 55 60
 Pro Tyr Ser Asn Ser Val Cys Val Arg Gly Lys Cys Val Arg Thr Gly
 65 70 75 80
 Cys Asp Ser Ile Ile Gly Ser Lys Leu Gln Tyr Asp Lys Cys Gly Val
 85 90 95
 Cys Gly Gly Asp Asn Ser Ser Cys Thr Lys Val Val Gly Thr Phe Asn
 100 105 110
 Lys Lys Ser Lys Gly Tyr Thr Asp Val Val Arg Ile Pro Glu Gly Ala
 115 120 125
 Thr His Ile Lys Val Arg Gln Phe Lys Ala Lys Asp Gln

130

135

140

<210> 19

<211> 637

<212> DNA

<213> Bos taurus

<400> 19

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ggaaaccctg gccatttgga gcaactacct ggccctgaag ctccccgatg gctcctatgc      60
cctcaacggt gaatacacgc tgatcccgtc cccacagac gtggtactgc ccggggccgt      120
cagcctgcgc tacagcgggg ccaactgcagc ctcggagaca ctgtcaggac acggggcccct      180
ggctgagccc ttaacgctgc aggtcctagt ggctggcaac ccgcagaacg cccgcctcag      240
atacagcttt ttcgtgccgc gaccgcgacc ggccccctcc acgccacgcc ccaactccca      300
ggactggctg cgccgcaagt cacagattct ggagatcctc cggcggcgct cctgggcccgg      360
caggaaataa cctcaccatc ccggctgccc tttctgggca cgggggcctc ggacttagct      420
gggtgaacga gagacctctg cagcggcctc accccgagac atcgtggggg aggggcttag      480
tgagccccgc ctctcctccc cgcgctaccg agcaggctgg ccctgccggg gtttcctgcc      540
ctggatggct ggtggatgga aggggctggg agattgtccc ctatctaaac tgccccctct      600
gccctgctgg tcacaggagg gagggggaag gcaggga                                637

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<210> 20

<211> 122

<212> PRT

<213> Bos taurus

<400> 20

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Glu Thr Leu Ala Ile Trp Ser Asn Tyr Leu Ala Leu Lys Leu Pro Asp
 1              5              10              15
Gly Ser Tyr Ala Leu Asn Gly Glu Tyr Thr Leu Ile Pro Ser Pro Thr
              20              25              30
Asp Val Val Leu Pro Gly Ala Val Ser Leu Arg Tyr Ser Gly Ala Thr
              35              40              45
Ala Ala Ser Glu Thr Leu Ser Gly His Gly Pro Leu Ala Glu Pro Leu
              50              55              60
Thr Leu Gln Val Leu Val Ala Gly Asn Pro Gln Asn Ala Arg Leu Arg
65              70              75              80
Tyr Ser Phe Phe Val Pro Arg Pro Arg Pro Val Pro Ser Thr Pro Arg
              85              90              95
Pro Thr Pro Gln Asp Trp Leu Arg Arg Lys Ser Gln Ile Leu Glu Ile
              100              105              110
Leu Arg Arg Arg Ser Trp Ala Gly Arg Lys
              115              120

```

<210> 21

<211> 1143

<212> DNA

<213> Homo sapien

<220>

<221> misc_feature

<222> (1)...(1143)

<223> n = A,T,C or G

<400> 21

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actcactata gggctcgtgc ggccgcccgg gcaggatatct ttaagcatcc cagcatcctc      60

```

```

aaccatcatca acatcggtgt ggtcaagggtg ctgcttctta gagatcgtga ctccggggccc 120
aagggtcaccg gcaatgcggc cctgacgctg cgcaacttct gtgcctggca gaagaagctg 180
aacaaagtga gtgacaagca ccccgagtag tgggacactg ccacccctct caccaggcag 240
gacctgtgtg gagccaccac ctgtgacacc ctgggcatgg ctgatgtggg taccatgtgt 300
gaccccaaga gaagctgtct tgtcattgag gacgatgggc ttccatcagc cttcaccact 360
gcccacgagc tggggccacgt gttcaacatg ccccatgaca atgtgaaagt ctgtgaggag 420
gtgtttggga agctccgagc caaccacatg atgtccccga ccctcatcca gatcgaccgt 480
gccaaaccct ggtcagcctg cagtgtgtcc atcatcaccg actttctgga cagcgggcac 540
ggtgactgcc tcctggacca acccagcaag cccatcttcc tgccgagnga tctgccgggc 600
gccagctaca ccctgagcca gcartgagag ctggcttttg gcgtgggctt caagccctgt 660
ccttacatgc agtactgcac caagctgtgg tgcaccggga aggccaaggg acagatgggtg 720
tgccaaaccc gccacttccc ctggggccgat ggcaccagtt gtggcgaggg caagttctgc 780
ctcaaagggg cctgcgtgga aaracacaac ctcaacaagc acaggggtgga tggttcctgg 840
gccaaatggg atccctatgg cccctgtctg cgcacatgtg gtgggggctg gcagctggcc 900
aggaggcagn tgcaccaacc ccancctctg ccaacngggg gcaagtactg cgagggagtg 960
agggtgaaat accgatcctg caacctggag ccctgcccc gctcagcctc cggaaagagc 1020
ttccgggagg agcagtgtga ggctttcaac ggctacaacc acagcaccaa ccggctcact 1080
ctgcgcgtgg catgggtgcc caagtactcc ggcgtgtctc cccgtgacaa gtgtaagctc 1140
atc 1143

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<210> 22

<211> 381

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (1)...(381)

<223> Xaa = Any Amino Acid

<400> 22

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Thr His Tyr Arg Ala Arg Ala Ala Arg Ala Gly Ile Phe Lys His
1          5          10          15
Pro Ser Ile Leu Asn Pro Ile Asn Ile Val Val Val Lys Val Leu Leu
20          25          30
Leu Arg Asp Arg Asp Ser Gly Pro Lys Val Thr Gly Asn Ala Ala Leu
35          40          45
Thr Leu Arg Asn Phe Cys Ala Trp Gln Lys Lys Leu Asn Lys Val Ser
50          55          60
Asp Lys His Pro Glu Tyr Trp Asp Thr Ala Ile Leu Phe Thr Arg Gln
65          70          75          80
Asp Leu Cys Gly Ala Thr Thr Cys Asp Thr Leu Gly Met Ala Asp Val
85          90          95
Gly Thr Met Cys Asp Pro Lys Arg Ser Cys Ser Val Ile Glu Asp Asp
100         105         110
Gly Leu Pro Ser Ala Phe Thr Thr Ala His Glu Leu Gly His Val Phe
115         120         125
Asn Met Pro His Asp Asn Val Lys Val Cys Glu Glu Val Phe Gly Lys
130         135         140
Leu Arg Ala Asn His Met Met Ser Pro Thr Leu Ile Gln Ile Asp Arg
145         150         155         160
Ala Asn Pro Trp Ser Ala Cys Ser Ala Ala Ile Ile Thr Asp Phe Leu
165         170         175
Asp Ser Gly His Gly Asp Cys Leu Leu Asp Gln Pro Ser Lys Pro Ile
180         185         190

```

Phe Leu Pro Xaa Asp Leu Pro Gly Ala Ser Tyr Thr Leu Ser Gln Gln
 195 200 205
 Cys Glu Leu Ala Phe Gly Val Gly Phe Lys Pro Cys Pro Tyr Met Gln
 210 215 220
 Tyr Cys Thr Lys Leu Trp Cys Thr Gly Lys Ala Lys Gly Gln Met Val
 225 230 235 240
 Cys Gln Thr Arg His Phe Pro Trp Ala Asp Gly Thr Ser Cys Gly Glu
 245 250 255
 Gly Lys Phe Cys Leu Lys Gly Ala Cys Val Glu Xaa His Asn Leu Asn
 260 265 270
 Lys His Arg Val Asp Gly Ser Trp Ala Lys Trp Asp Pro Tyr Gly Pro
 275 280 285
 Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Leu Ala Arg Arg Gln Xaa
 290 295 300
 His Gln Pro Xaa Pro Leu Pro Thr Gly Gly Lys Tyr Cys Glu Gly Val
 305 310 315 320
 Arg Val Lys Tyr Arg Ser Cys Asn Leu Glu Pro Cys Pro Ser Ser Ala
 325 330 335
 Ser Gly Lys Ser Phe Arg Glu Glu Gln Cys Glu Ala Phe Asn Gly Tyr
 340 345 350
 Asn His Ser Thr Asn Arg Leu Thr Leu Ala Val Ala Trp Val Pro Lys
 355 360 365
 Tyr Ser Gly Val Ser Pro Arg Asp Lys Cys Lys Leu Ile
 370 375 380

<210> 23

<211> 297

<212> DNA

<213> Rattus norvegicus

<400> 23

tccgccttc	cgggaggaac	agtgtgaaaa	atataatgcc	tacaaccaca	cggacctgga	60
tgggaatttc	cttcagtggg	tcccaata	ctcaggagt	tcccccgag	accgatgcaa	120
actgttttgc	agagcccg	ggaggagtga	gttcaaagt	tttgaaacta	aggtgatcga	180
tggcactctg	tgcggaccg	atactctggc	catctgtgtg	cggggacagt	gcgttaaggc	240
tggctgtgac	catgtggtga	actcacctaa	gaagctggac	aagtgcggtg	tctgtgtg	297

<210> 24

<211> 98

<212> PRT

<213> Rattus norvegicus

<400> 24

Pro	Pro	Phe	Arg	Glu	Glu	Gln	Cys	Glu	Lys	Tyr	Asn	Ala	Tyr	Asn	His
1			5						10					15	
Thr	Asp	Leu	Asp	Gly	Asn	Phe	Leu	Gln	Trp	Val	Pro	Lys	Tyr	Ser	Gly
			20					25					30		
Val	Ser	Pro	Arg	Asp	Arg	Cys	Lys	Leu	Phe	Cys	Arg	Ala	Arg	Gly	Arg
			35				40					45			
Ser	Glu	Phe	Lys	Val	Phe	Glu	Thr	Lys	Val	Ile	Asp	Gly	Thr	Leu	Cys
			50			55				60					
Gly	Pro	Asp	Thr	Leu	Ala	Ile	Cys	Val	Arg	Gly	Gln	Cys	Val	Lys	Ala
65				70					75					80	
Gly	Cys	Asp	His	Val	Val	Asn	Ser	Pro	Lys	Lys	Leu	Asp	Lys	Cys	Gly
			85					90						95	

Ile Cys

<210> 25
 <211> 823
 <212> DNA
 <213> Rattus norvegicus

<400> 25
 cccctggatg tgggtcaaagt gcagtcggaa gtacatcacc gagttcttag acactgggta 60
 tggagagtgc ttgttaaagt aacctcaatc caggacctat cctttgcctt cccaactgcc 120
 cggccttctc tacaacgtga ataaacaatg tgaactgatt tttggaccag gctctcaagt 180
 gtgcccataat atgatgcagt gcagacggct ctggtgcaat aacgtggatg gagcacacaa 240
 aggtgcagg actcagcaca cgccctgggc agatggaacc gagtgtgagc ctggaaagca 300
 ctgcaagttt ggattctgtg ttcccaaaga aatggagggc cctgcaattg atggatcctg 360
 gggaagtttg agtcactttg gggcctgctc aagaacatgt ggaggaggca tcagaacagc 420
 catcagagag tgcaacagac cagagccaaa aaatggtggg aggtactgtg tagggaggag 480
 aatraagtgc aaatccttgc acaccgagcc ctgcccgaag cacaagcgag acttccgtga 540
 ggagcagtgt gcttactttg acggcaagca tttcaacatc aatggtctgc tgcccagtg 600
 acgctgggtc cctaagtaca gtggaatttt gatgaaggac cgatgcaagt tgttctgcag 660
 agtggcagga aacacagcct actaccagct tcgagacaga gtgattgacg gaacccctg 720
 tggccaggac acaaatgaca tctgtgtcca aggcctttgc cggcaagctg gatgtgatca 780
 tactttaaac tcaaaggccc ggaaagataa atgtgggatt tgt 823

<210> 26
 <211> 274
 <212> PRT
 <213> Rattus norvegicus

<220>
 <221> VARIANT
 <222> (1)...(274)
 <223> Xaa = Any Amino Acid

<400> 26
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 1 5 10 15
 Asp Thr Gly Tyr Gly Glu Cys Leu Leu Asn Glu Pro Gln Ser Arg Thr
 20 25 30
 Tyr Pro Leu Pro Ser Gln Leu Pro Gly Leu Leu Tyr Asn Val Asn Lys
 35 40 45
 Gln Cys Glu Leu Ile Phe Gly Pro Gly Ser Gln Val Cys Pro Tyr Met
 50 55 60
 Met Gln Cys Arg Arg Leu Trp Cys Asn Asn Val Asp Gly Ala His Lys
 65 70 75 80
 Gly Cys Arg Thr Gln His Thr Pro Trp Ala Asp Gly Thr Glu Cys Glu
 85 90 95
 Pro Gly Lys His Cys Lys Phe Gly Phe Cys Val Pro Lys Glu Met Glu
 100 105 110
 Gly Pro Ala Ile Asp Gly Ser Trp Gly Ser Trp Ser His Phe Gly Ala
 115 120 125
 Cys Ser Arg Thr Cys Gly Gly Gly Ile Arg Thr Ala Ile Arg Glu Cys
 130 135 140
 Asn Arg Pro Glu Pro Lys Asn Gly Gly Arg Tyr Cys Val Gly Arg Arg
 145 150 155 160

[illegible]

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<210> 27
<211> 1073
<212> PRT
<213> Homo sapien
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<400> 27															
Met 1	Gln	Phe	Val	Ser 5	Trp	Ala	Thr	Leu	Leu 10	Thr	Leu	Leu	Val	Arg 15	Asp
Leu	Ala	Glu	Met 20	Gly	Ser	Pro	Asp 25	Ala	Ala	Ala	Ala	Val	Arg 30	Lys	Asp
Arg	Leu	His 35	Pro	Arg	Gln	Val	Lys 40	Leu	Leu	Glu	Thr	Leu	Gly	Glu	Tyr
Glu	Ile 50	Val	Ser	Pro	Ile	Arg 55	Val	Asn	Ala	Leu	Gly 60	Glu	Pro	Phe	Pro
Thr 65	Asn	Val	His	Phe	Lys 70	Arg	Thr	Arg	Arg	Ser 75	Ile	Asn	Ser	Ala	Thr 80
Asp	Pro	Trp	Pro	Ala 85	Phe	Ala	Ser	Ser	Ser	Ser	Ser	Ser	Thr	Ser	Ser
Gln	Ala	His	Tyr 100	Arg	Leu	Ser	Ala	Phe 105	Gly	Gln	Gln	Phe	Leu	Phe	Asn
Leu	Thr	Ala	Asn 115	Ala	Gly	Phe	Ile 120	Ala	Pro	Leu	Phe	Thr	Val	Thr	Leu
Leu	Gly	Thr	Pro	Gly	Val	Asn 135	Gln	Thr	Lys	Phe	Tyr 140	Ser	Glu	Glu	Glu
Ala 145	Glu	Leu	Lys	His	Cys 150	Phe	Tyr	Lys	Gly	Tyr	Val	Asn	Thr	Asn	Ser 160
Glu	His	Thr	Ala	Val 165	Ile	Ser	Leu	Cys	Ser	Gly	Met	Leu	Gly	Thr	Phe
Arg	Ser	His	Asp 180	Gly	Asp	Tyr	Phe	Ile 185	Glu	Pro	Leu	Gln	Ser	Met	Asp
Glu	Gln	Glu	Asp 195	Glu	Glu	Glu	Gln	Asn 200	Lys	Pro	His	Ile	Ile	Tyr	Arg
Arg	Ser	Ala	Pro	Gln	Arg	Glu 215	Pro	Ser	Thr	Gly	Arg	His	Ala	Cys	Asp
Thr 225	Ser	Glu	His	Lys	Asn 230	Arg	His	Ser	Lys	Asp	Lys	Lys	Lys	Thr	Arg 240
Ala	Arg	Lys	Trp	Gly 245	Glu	Arg	Ile	Asn	Leu	Ala	Gly	Asp	Val	Ala	Ala
Leu	Asn	Ser	Gly	Leu	Ala	Thr	Glu	Ala	Phe	Ser	Ala	Tyr	Gly	Asn	Lys

			260					265					270		
Thr	Asp	Asn	Thr	Arg	Glu	Lys	Arg	Thr	His	Arg	Arg	Thr	Lys	Arg	Phe
		275					280					285			
Leu	Ser	Tyr	Pro	Arg	Phe	Val	Glu	Val	Leu	Val	Val	Ala	Asp	Asn	Arg
	290					295					300				
Met	Val	Ser	Tyr	His	Gly	Glu	Asn	Leu	Gln	His	Tyr	Ile	Leu	Thr	Leu
305					310					315					320
Met	Ser	Ile	Val	Ala	Ser	Ile	Tyr	Lys	Asp	Pro	Ser	Ile	Gly	Asn	Leu
			325					330						335	
Ile	Asn	Ile	Val	Ile	Val	Asn	Leu	Ile	Val	Ile	His	Asn	Glu	Gln	Asp
			340					345					350		
Gly	Pro	Ser	Ile	Ser	Phe	Asn	Ala	Gln	Thr	Thr	Leu	Lys	Asn	Leu	Cys
	355					360						365			
Gln	Trp	Gln	His	Ser	Lys	Asn	Ser	Pro	Gly	Gly	Ile	His	His	Asp	Thr
	370				375						380				
Ala	Val	Leu	Leu	Thr	Arg	Gln	Asp	Ile	Cys	Arg	Ala	His	Asp	Lys	Cys
385					390					395					400
Asp	Thr	Leu	Gly	Leu	Ala	Glu	Leu	Gly	Thr	Ile	Cys	Asp	Pro	Tyr	Arg
			405					410						415	
Ser	Cys	Ser	Ile	Ser	Glu	Asp	Ser	Gly	Leu	Ser	Thr	Ala	Phe	Thr	Ile
			420					425					430		
Ala	His	Glu	Leu	Gly	His	Val	Phe	Asn	Met	Pro	His	Asp	Asp	Asn	Asn
	435					440						445			
Lys	Cys	Lys	Glu	Glu	Gly	Val	Lys	Ser	Pro	Gln	His	Val	Met	Ala	Pro
	450				455					460					
Thr	Leu	Asn	Phe	Tyr	Thr	Asn	Pro	Trp	Met	Trp	Ser	Lys	Cys	Ser	Arg
465					470					475					480
Lys	Tyr	Ile	Thr	Glu	Phe	Leu	Asp	Thr	Gly	Tyr	Gly	Glu	Cys	Leu	Leu
			485					490						495	
Asn	Glu	Pro	Glu	Ser	Arg	Pro	Tyr	Pro	Leu	Pro	Val	Gln	Leu	Pro	Gly
			500					505					510		
Ile	Leu	Tyr	Asn	Val	Asn	Lys	Gln	Cys	Glu	Leu	Ile	Phe	Gly	Pro	Gly
		515					520					525			
Ser	Gln	Val	Cys	Pro	Tyr	Met	Met	Gln	Cys	Arg	Arg	Leu	Trp	Cys	Asn
	530					535					540				
Asn	Val	Asn	Gly	Val	His	Lys	Gly	Cys	Arg	Thr	Gln	His	Thr	Pro	Trp
545					550					555					560
Ala	Asp	Gly	Thr	Glu	Cys	Glu	Pro	Gly	Lys	His	Cys	Lys	Tyr	Gly	Phe
			565					570						575	
Cys	Val	Pro	Lys	Glu	Met	Asp	Val	Pro	Val	Thr	Asp	Gly	Ser	Trp	Gly
			580					585					590		
Ser	Trp	Ser	Pro	Phe	Gly	Thr	Cys	Ser	Arg	Thr	Cys	Gly	Gly	Gly	Ile
		595					600					605			
Lys	Thr	Ala	Ile	Arg	Glu	Cys	Asn	Arg	Pro	Glu	Pro	Lys	Asn	Gly	

Val Ile Asp Gly Thr Pro Cys Gly Gln Asp Thr Asn Asp Ile Cys Val
 705 710 715 720
 Gln Gly Leu Cys Arg Gln Ala Gly Cys Asp His Val Leu Asn Ser Lys
 725 730 735
 Ala Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asn Ser Ser Cys
 740 745 750
 Lys Thr Val Ala Gly Thr Phe Asn Thr Val His Tyr Gly Tyr Asn Thr
 755 760 765
 Val Val Arg Ile Pro Ala Gly Ala Thr Asn Ile Asp Val Arg Gln His
 770 775 780
 Ser Phe Ser Gly Glu Thr Asp Asp Asp Asn Tyr Leu Ala Leu Ser Ser
 785 790 795 800
 Ser Lys Gly Glu Phe Leu Leu Asn Gly Asn Phe Val Val Thr Met Ala
 805 810 815
 Lys Arg Glu Ile Arg Ile Gly Asn Ala Val Val Glu Tyr Ser Gly Ser
 820 825 830
 Glu Thr Ala Val Glu Arg Ile Asn Ser Thr Asp Arg Ile Glu Gln Glu
 835 840 845
 Leu Leu Leu Gln Val Leu Ser Val Gly Lys Leu Tyr Asn Pro Asp Val
 850 855 860
 Arg Tyr Ser Phe Asn Ile Pro Ile Glu Asp Lys Pro Gln Gln Phe Tyr
 865 870 875 880
 Trp Asn Ser His Gly Pro Trp Gln Ala Cys Ser Lys Pro Cys Gln Gly
 885 890 895
 Glu Arg Lys Arg Lys Leu Val Cys Thr Arg Glu Ser Asp Gln Leu Thr
 900 905 910
 Val Ser Asp Gln Arg Cys Asp Arg Leu Pro Gln Pro Gly His Ile Thr
 915 920 925
 Glu Pro Cys Gly Thr Asp Cys Asp Leu Arg Trp His Val Ala Ser Arg
 930 935 940
 Ser Glu Cys Ser Ala Gln Cys Gly Leu Gly Tyr Arg Thr Leu Asp Ile
 945 950 955 960
 Tyr Cys Ala Lys Tyr Ser Arg Leu Asp Gly Lys Thr Glu Lys Val Asp
 965 970 975
 Asp Gly Phe Cys Ser Ser His Pro Lys Pro Ser Asn Arg Glu Lys Cys
 980 985 990
 Ser Gly Glu Cys Asn Thr Gly Gly Trp Arg Tyr Ser Ala Trp Thr Glu
 995 1000 1005
 Cys Lys Ser Lys Ser Cys Asp Gly Gly Thr Gln Arg Arg Arg Ala Ile
 1010 1015 1020
 Cys Val Asn Thr Arg Asn Asp Val Leu Asp Asp Ser Lys Cys Thr His
 1025 1030 1035 1040
 Gln Glu Lys Val Thr Ile Gln Arg Cys Ser Glu Phe Pro Cys Pro Gln
 1045 1050 1055
 Trp Lys Ser Gly Asp Trp Ser Glu Val Arg Trp Glu Gly Cys Tyr Phe
 1060 1065 1070
 Pro

<210> 28

<211> 951

<212> PRT

<213> Mus musculus

<400> 28

Met Gly Asp Val Gln Arg Ala Ala Arg Ser Arg Gly Ser Leu Ser Ala

1	5	10	15
His Met Leu Leu Leu Leu Leu Ala Ser Ile Thr Met Leu Leu Cys Ala			
	20	25	30
Arg Gly Ala His Gly Arg Pro Thr Glu Glu Asp Glu Glu Leu Val Leu			
	35	40	45
Pro Ser Leu Glu Arg Ala Pro Gly His Asp Ser Thr Thr Thr Arg Leu			
	50	55	60
Arg Leu Asp Ala Phe Gly Gln Gln Leu His Leu Lys Leu Gln Pro Asp			
65	70	75	80
Ser Gly Phe Leu Ala Pro Gly Phe Thr Leu Gln Thr Val Gly Arg Ser			
	85	90	95
Pro Gly Ser Glu Ala Gln His Leu Asp Pro Thr Gly Asp Leu Ala His			
	100	105	110
Cys Phe Tyr Ser Gly Thr Val Asn Gly Asp Pro Gly Ser Ala Ala Ala			
	115	120	125
Leu Ser Leu Cys Glu Gly Val Arg Gly Ala Phe Tyr Leu Gln Gly Glu			
	130	135	140
Glu Phe Phe Ile Gln Pro Ala Pro Gly Val Ala Thr Glu Arg Leu Ala			
145	150	155	160
Pro Ala Val Pro Glu Glu Glu Ser Ser Ala Arg Pro Gln Phe His Ile			
	165	170	175
Leu Arg Arg Arg Arg Arg Gly Ser Gly Gly Ala Lys Cys Gly Val Met			
	180	185	190
Asp Asp Glu Thr Leu Pro Thr Ser Asp Ser Arg Pro Glu Ser Gln Asn			
	195	200	205
Thr Arg Asn Gln Trp Pro Val Arg Asp Pro Thr Pro Gln Asp Ala Gly			
	210	215	220
Lys Pro Ser Gly Pro Gly Ser Ile Arg Lys Lys Arg Phe Val Ser Ser			
225	230	235	240
Pro Arg Tyr Val Glu Thr Met Leu Val Ala Asp Gln Ser Met Ala Asp			
	245	250	255
Phe His Gly Ser Gly Leu Lys His Tyr Leu Leu Thr Leu Phe Ser Val			
	260	265	270
Ala Ala Arg Phe Tyr Lys His Pro Ser Ile Arg Asn Ser Ile Ser Leu			
	275	280	285
Val Val Val Lys Ile Leu Val Ile Tyr Glu Glu Gln Lys Gly Pro Glu			
	290	295	300
Val Thr Ser Asn Ala Ala Leu Thr Leu Arg Asn Phe Cys Asn Trp Gln			
305	310	315	320
Lys Gln His Asn Ser Pro Ser Asp Arg Asp Pro Glu His Tyr Asp Thr			
	325	330	335
Ala Ile Leu Phe Thr Arg Gln Asp Leu Cys Gly Ser His Thr Cys Asp			
	340	345	350
Thr Leu Gly Met Ala Asp Val Gly Thr Val Cys Asp Pro Ser Arg Ser			
	355	360	365
Cys Ser Val Ile Glu Asp Asp Gly Leu Gln Ala Ala Phe Thr Thr Ala			
	370	375	380
His Glu Leu Gly His Val Phe Asn Met Pro His Asp Asp Ala Lys His			
385	390	395	400
Cys Ala Ser Leu Asn Gly Val Thr Gly Asp Ser His Leu Met Ala Ser			
	405	410	415
Met Leu Ser Ser Leu Asp His Ser Gln Pro Trp Ser Pro Cys Ser Ala			
	420	425	430
Tyr Met Val Thr Ser Phe Leu Asp Asn Gly His Gly Glu Cys Leu Met			
	435	440	445

Asp	Lys	Pro	Gln	Asn	Pro	Ile	Lys	Leu	Pro	Ser	Asp	Leu	Pro	Gly	Thr
450						455					460				
Leu	Tyr	Asp	Ala	Asn	Arg	Gln	Cys	Gln	Phe	Thr	Phe	Gly	Glu	Glu	Ser
465					470					475					480
Lys	His	Cys	Pro	Asp	Ala	Ala	Ser	Thr	Cys	Thr	Thr	Leu	Trp	Cys	Thr
				485					490					495	
Gly	Thr	Ser	Gly	Gly	Leu	Leu	Val	Cys	Gln	Thr	Lys	His	Phe	Pro	Trp
			500					505					510		
Ala	Asp	Gly	Thr	Ser	Cys	Gly	Glu	Gly	Lys	Trp	Cys	Val	Ser	Gly	Lys
		515					520					525			
Cys	Val	Asn	Lys	Thr	Asp	Met	Lys	His	Phe	Ala	Thr	Pro	Val	His	Gly
530					535						540				
Ser	Trp	Gly	Pro	Trp	Gly	Pro	Trp	Gly	Asp	Cys	Ser	Arg	Thr	Cys	Gly
545					550				555						560
Gly	Gly	Val	Gln	Tyr	Thr	Met	Arg	Glu	Cys	Asp	Asn	Pro	Val	Pro	Lys
				565					570					575	
Asn	Gly	Gly	Lys	Tyr	Cys	Glu	Gly	Lys	Arg	Val	Arg	Tyr	Arg	Ser	Cys
			580					585					590		
Asn	Ile	Glu	Asp	Cys	Pro	Asp	Asn	Gly	Lys	Thr	Phe	Arg	Glu	Glu	
		595					600				605				
Gln	Cys	Glu	Ala	His	Asn	Glu	Phe	Ser	Lys	Ala	Ser	Phe	Gly	Asn	Glu
610						615					620				
Pro	Thr	Val	Glu	Trp	Thr	Pro	Lys	Tyr	Ala	Gly	Val	Ser	Pro	Lys	Asp
625					630					635					640
Arg	Cys	Lys	Leu	Thr	Cys	Glu	Ala	Lys	Gly	Ile	Gly	Tyr	Phe	Phe	Val
				645					650					655	
Leu	Gln	Pro	Lys	Val	Val	Asp	Gly	Thr	Pro	Cys	Ser	Pro	Asp	Ser	Thr
			660					665					670		
Ser	Val	Cys	Val	Gln	Gly	Gln	Cys	Val	Lys	Ala	Gly	Cys	Asp	Arg	Ile
		675					680					685			
Ile	Asp	Ser	Lys	Lys	Lys	Phe	Asp	Lys	Cys	Gly	Val	Cys	Gly	Gly	Asn
	690					695					700				
Gly	Ser	Thr	Cys	Lys	Lys	Met	Ser	Gly	Ile	Val	Thr	Ser	Thr	Arg	Pro
705					710					715					720
Gly	Tyr	His	Asp	Ile	Val	Thr	Ile	Pro	Ala	Gly	Ala	Thr	Asn	Ile	Glu
				725					730					735	
Val	Lys	His	Arg	Asn	Gln	Arg	Gly	Ser	Arg	Asn	Asn	Gly	Ser	Phe	Leu
			740					745					750		
Ala	Ile	Arg	Ala	Ala	Asp	Gly	Thr	Tyr	Ile	Leu	Asn	Gly	Asn	Phe	Thr
		755					760					765			
Leu	Ser	Thr	Leu	Glu	Gln	Asp	Leu	Thr	Tyr	Lys	Gly	Thr	Val	Leu	Arg
770						775					780				
Tyr	Ser	Gly	Ser	Ser	Ala	Ala	Leu	Glu	Arg	Ile	Arg	Ser	Phe	Ser	Pro
785					790					795					800
Leu	Lys	Glu	Pro	Leu	Thr	I									

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<211> 6
<212> PRT
<213> Unknown

<220>
<223> Semiconserved sequence of ADAMTS protein domain
that binds to the extracellular matrix

<400> 32
Phe Arg Glu Glu Gln Cys
1 5

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<211> 18
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<400> 33
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<221> misc_feature
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<400> 34
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18

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<220>
<223> Consensus catalytic sequence site based on ADAM
and snake venom metalloproteases

<221> VARIANT
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motif of ADAM-TS family members

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<220>
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motif of ADAM-TS family members

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1 5

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<400> 38

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24

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21

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21

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aaaatcacag gttggcagcg g

21

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5

10

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<211> 12

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1 5 10

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<213> Homo sapien

<400> 49

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1 5 10

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<212> PRT

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<212> PRT

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and snake venom metalloproteases

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<223> Xaa = Any Amino Acid

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